CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761194Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 109569

MEETING MINUTES

Genzyme Corporation
Attention: Jane Aoyagi
Senior Director, Global Regulatory Affairs
55 Corporate Drive
Bridgewater, NJ 08807

Dear Ms. Aoyagi:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GZ402666.

We also refer to the telecon between representatives of your firm and the FDA on June 30, 2020. The purpose of the meeting was to discuss key components and obtain procedural and regulatory guidance for your Biologics License Application (BLA) submission.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jenny Doan, Regulatory Project Manager at (301) 796-1023.

Sincerely,

{See appended electronic signature page}

Lisa Soule, MD
Associate Director
Division of Rare Diseases and Medical Genetics
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: June 30, 2020; 11:15 AM – 12:15 PM ET
Meeting Location: Teleconference

Application Number: IND 109569
Product Name: GZ402666

Indication: long-term use as an enzyme replacement therapy (ERT) for the treatment of patients with Pompe disease (acid α-glucosidase deficiency)
Sponsor Name: Genzyme Corporation

Meeting Chair: Lisa Soule, MD
Meeting Recorder: Jenny Doan, RPM

FDA ATTENDEES

Division of Rare Diseases and Medical Genetics
Kathleen Donohue, MD, Director (Acting)
Lisa Soule, MD, Associate Director
Dina Zand, MD, Medical Reviewer
Jacqueline Karp, MD, Medical Reviewer

Division of Pharm/Tox of Rare Diseases, Pediatric, Urologic and Reproductive Medicine
Emmanuel Akinshola, PhD, Toxicologist

Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine
Jenny Doan, MSN, BSN, PMP, Regulatory Health Project Manager

Office of Clinical Pharmacology/Division of Translational and Precision Medicine
Jie (Jack) Wang, PhD, Clinical Pharmacology Team Leader
Christine Hon, PhD, Clinical Pharmacology Reviewer
Joshua Cinicola, Pharmacy Student
Jerry Sicalo, Pharmacy Student

Office of Biostatistics/ Division of Biometrics IV
Yan Wang, PhD, Biostatistics Team Leader
Wonyul Lee, PhD, Biostatistics Reviewer

Office of Biotechnology Products
Susan Kirshner, PhD, CMC Team Leader

SPONSOR ATTENDEES

Kristina An Haack, MD, Global Project Head, Global Clinical Development
Karin Knobe, MD, PhD, Associate Professor - Therapeutic Area Head, Rare Diseases and Rare Blood Disorders, Clinical Development
Meehyung Cho, PhD, Global Head of Biostatistics in Rare Disease, MS Neurology
Tianyue Zhou, PhD, Director, Biostatistics
John Caminis, MD, Assistant Vice President - Therapeutic Area Head, Rare Diseases, Global Pharmacovigilance
Judith Johnson, MD, Senior Director, Global Pharmacovigilance
Priti Lad, PharmD, Senior Director, Global Regulatory Affairs NA
Jane Aoyagi, BSc, Senior Director, Global Regulatory Affairs NA
Peggy Sung, MA, Associate Director, Global Regulatory Affairs
Arden Tesmer, MS, Manager, Global Regulatory Affairs NA
Marc J. DeLuca, MEng, HSE, US Risk Management Lead
Fabrice Hurbin, PharmD, Clinical Pharmacokinetics
Celine Thierens, Global CMC Biologics
Tonia R. Holverson, MS, PhD, RAC, GRA CMC Biologics
Susan Richards, PhD, FAAPS, Vice President, Translational Medicine and Early Development
Patrick Miossec, MD, Director, Clinical Investigations

1.0 BACKGROUND

FDA Regulatory Background

IND 109569 was initially submitted to the FDA on March 28, 2013, for the development of GZ402666, also referred to as avalglucosidase alfa, a second-generation enzyme replacement therapy (ERT) for the intravenous (IV) treatment of patients with a confirmed diagnosis of Pompe disease. The clinical development program was designed to demonstrate clinical benefit of GZ402666 over the first generation ERT, alglucosidase alfa. Some relevant regulatory milestones are highlighted below:

November 19, 2013	Orphan Drug Designation granted (DRU-2013-4119)
August 14, 2019	Fast Track Designation granted
June 3, 2020	Breakthrough Therapy Designation granted

A type C meeting was held on February 20, 2020, to discuss the statistical analysis plan (SAP) for Study ECF 14028. Based on the meeting discussion, the sponsor submitted a revised SAP proposing the treatment-policy estimand estimated by a repeated measure mixed model (MMRM) for the primary estimand on February 28, 2020. Preliminarily, we

considered this estimand acceptable but stated that the final acceptability of its estimation based on the MMRM would ultimately be determined upon review of the study data (refer to advice letter dated April 13, 2020). This communication also contained requests regarding the assessment of immunogenicity for GZ402666.

Additional studies to support use in patients diagnosed with infantile onset Pompe disease (IOPD) were discussed at the type C meeting held on June 9, 2020. Refer to the meeting minutes dated June 16, 2020, for details.

On May 6, 2020, Genzyme requested a pre-BLA meeting to discuss their proposed plan for a 351(a) Biologic Licensed Application (BLA) for GZ402666. On May 6, 2020, FDA granted this as a type B pre-BLA teleconference. The meeting briefing package was received on May 29, 2020. FDA sent Preliminary Comments on June 23, 2020.

Genzyme plans to submit a rolling review BLA for GZ402666 that includes the nonclinical module submission in July 2020 and submission of all the remaining modules in September 2020. The rolling review submission request was granted on June 24, 2020.

FDA Clinical Background

Pompe disease (also known as acid maltase deficiency or glycogen storage disease [GSD] type II) is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid alpha-glucosidase (GAA), an enzyme that degrades glycogen. In this lysosomal disorder, glycogen accumulation in affected tissue (primarily skeletal and/or cardiac muscle) can result in progressive hypotonia, respiratory failure, and cardiomyopathy. The disease spectrum ranges from the severe, rapidly progressive infantile-onset Pompe disease (IOPD), and the slowly progressive, heterogeneous late-onset Pompe disease (LOPD).

In the U.S., the first ERT for Pompe disease was approved in 2006 (Myozyme for IOPD; Genzyme) and in 2010 (Lumizyme for LOPD; Genzyme). Lumizyme is the current standard of care for both IOPD and LOPD with labeled dosing of 20 mg/kg IV infusion every two weeks. The literature currently describes the natural history of disease on ERT to plateau or worsen in pulmonary or gross motor function after anywhere from 2-5 years on current standard of care (ERT), suggesting the need to develop second generation therapies for both IOPD and LOPD.

GZ402666, or avalglucosidase alfa, is engineered to contain the same protein sequence as alglucosidase alfa (Myozyme/Lumizyme) in addition to post-translational modifications of extra mannose-6-phosphate residues, postulated by the Sponsor to improve binding and cellular uptake in GAA-deficient cells.

To support the marketing approval of GZ402666, Genzyme intends to submit data from a total of 4 completed and ongoing clinical studies, summarized in Table 1.

Table 1: GZ402666 Development Program Studies to be Submitted in the BLA

Trial # /Title	Primary Objectives	Study Design	Dose	# Subjects	Completion Status
TDR12857 NEO1	PK, PD, safety Exploratory efficacy	Phase 1, OL, AD, in TN or TE adults	5,10, 20 mg/kg QOW 13 infusions	24 patients (LOPD)	Completed
LTS13769 NEO-EXT	PK, PD, safety, exploratory efficacy	OL extension TDR12857 adults	20 mg/kg QOW	19 patients (LOPD)	Ongoing
EFC14028 COMET	Efficacy, *Primary: FVC % predicted* *Secondary: (1st key) 6MWD* safety, PK, PD	Phase 3, DB with active comparator in patients ≥ 3 years to adults	20 mg/kg QOW for 12 months or more (extension)	~100 patients (LOPD)	Ongoing
ACT14132 Mini-COMET	Safety, PK, PD, Exploratory efficacy	Phase 2, OL for patients (<18 years) with clinical decline or sub-optimal response on current standard of care	20 mg/kg or 40 mg/kg QOW 24 weeks + extension	22 patients (IOPD)	Ongoing

Source: IND 109569 Meeting request
OL = open label; AD = ascending dose; TN = treatment naïve; TE = treatment experienced; R = randomized; DB = double blind; QOW = every other week; PK = pharmacokinetic; PD = pharmacodynamic

The meeting discussion will be based upon these four studies and their contributions toward the possible registration of GZ402666 as a second generation ERT for the treatment of patients diagnosed with Pompe disease (b) (4)

2.0 DISCUSSION

FDA Introductory Comment:
As reviewed in the recent request for breakthrough therapy designation (BTD), the preliminary results from Study EFC14028 appear supportive of improved efficacy of avalglucosidase alfa over alglucosidase alfa in treatment-naïve LOPD patients. The preliminary data provided in this meeting package describing treatment-experienced IOPD patients is also encouraging. Because the Division believes that efficacy from LOPD cannot be extrapolated to IOPD patients, the indication for avalglucosidase alfa will be considered based upon the data submitted for IOPD and LOPD patients to the BLA and will not include patients aged 0-6 months of age (refer to the meeting minutes dated June 16, 2020, for the type C meeting on June 9, 2020).

Question 1:
Does the Agency agree that the proposed clinical data package is sufficient to warrant filing and review of an initial BLA for the indication of Pompe Disease?

FDA Response to Question 1:
Although the fileability of the application will be determined after the initial review of the submission, the proposed clinical data package appears reasonable to support the assessment of efficacy for treatment-naïve and treatment-experienced LOPD patients and treatment-experienced IOPD patients. However, as discussed in the in the type C teleconference on June 9, 2020, (b) (4)

Meeting Discussion: ***No further discussion required.***

Question 2:
Does the Agency agree with the proposed dosing recommendations for Late Onset Pompe disease (b) (4) *patients based on the data for the two doses used in studies ACT14132 and EFC14028 for an indication for Pompe Disease?*

FDA Response to Question 2:
You propose the following dosing recommendations:

Late-onset Pompe disease patients

- *The recommended dose of avalglucosidase alfa is 20 mg/kg of body weight administered every other week as intravenous infusion.*

(b) (4)

In general, we recommend that the dosing regimen(s) with the most favorable benefit/risk profile be selected based on dose- or exposure-response (E-R) relationships for both efficacy and safety. You should provide dose justification to address whether the proposed dosing regimens are appropriate for the general patient population of the proposed indication, and to address whether an alternative dosing regimen may be necessary for subpopulations based on intrinsic and extrinsic factors. We have the following recommendations and comments to help you provide dose justification in the BLA submission:

1. The impact of immunogenicity on PK, PD, efficacy and safety of avaglucosidase alfa will be helpful to determine the optimal dosing regimens. For the evaluation of the immunogenicity impact, we recommend that you include results of between-subject comparison (i.e., between anti-drug antibody [ADA]-positive

subjects and ADA-negative subjects) as well as within-subject comparison (i.e., before becoming ADA-positive and after ADA-positive).

2. We acknowledge that you plan to conduct population PK analysis of avalglucosidase alfa to support PK and dose selection of your BLA. We encourage you to include subjects' ADA status as a covariate in the population PK analysis on an exploratory basis to evaluate the impact of ADA on PK of avaglucosidase alfa. In the population PK analysis, further explore the necessity of treating the subject ADA status as a time-varying variable for ADA-positive subjects with or without the ADA titer data.

3. Submit a study report describing E-R relationships for efficacy (including pharmacodynamic biomarkers) and safety in the target patient population. Considering the small number of subjects in your clinical program, we recommend that you conduct E-R analysis at both population and individual levels for subjects who received multiple dose levels during dose escalation in clinical trials. (b) (4)

4. Refer to the "Model/Data Format"[1] for general guidance on submitting pharmacometric data. Also refer to the FDA guidance for additional information related to population PK[2,3] and E-R analyses.[2,4]

   We recommend that you include the following in the population PK analysis report:

   - Standard model diagnostic plots
   - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
   - Model parameter names and units in tables
   - Summary of the report describing the clinical application of modeling results

   Also submit the following information and data to support the population PK analysis:

[1] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/modeldata-format

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] https://www.fda.gov/media/128793/download

[4] https://www.fda.gov/media/71277/download

- SAS transport files (*.xpt) for all datasets used for model development and validation
- A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Ultimately, the dosing recommendations will need to be supported by both PK and clinical data. (b) (4)

Meeting Discussion: ***Refer to attached Sponsor's response to FDA Preliminary Comments.***

The Sponsor clarified the following:

- ***No patients enrolled in Study EFC14028 (LOPD) received immune tolerance induction (ITI) therapies.***
- ***Four patients enrolled in Study ACT14132 (IOPD) received ITI therapies: two CRIM-negative patients and two CRIM-positive patients. The CRIM-negative patients will be analyzed separately for immunogenicity and the CRIM-positive patients will be identified in the Clinical Study reports (CSR). The Sponsor agreed to provide information about ITI therapies received by the IOPD subjects.***
- ***The clinical and laboratory-based criteria used to justify dose reduction and dose increases will be provided and explained.***

Regarding the Sponsor's approach to assess the impact of immunogenicity on PK, PD, safety, and efficacy in LOPD based on ADA peak titer groups (low: ≤ 800; intermediate: 1600-6400; and high: ≥ 12800), the Agency recommended that the Sponsor provide justifications in the BLA for the selected ADA peak titer cutoff values.

The Sponsor clarified that the within-subject comparison of PK before and after developing ADA is limited because PK profile assessment was performed at Week 1 and Week 49 with no mid-point PK evaluation in LOPD (i.e., Study EFC14028). See the Post-Meeting Comments below.

The Sponsor and the Agency discussed the submission of PK and immunogenicity datasets. See the Post-Meeting Comments below.

The Agency stated that the Agency might have additional comments at the time of BLA review.

Post-Meeting Comments:
We received your post-meeting "Clinical Pharmacology Clarification for Meeting Minutes" via email on July 1, 2020. We note that there were 51 naïve LOPD patients randomized to the avalglucosidase alfa arm in the blinded treatment period of EFC14082 who had full PK profile assessments on Day 1/2 and Week 49. Because the majority of patients in EFC14028 developed anti-drug antibodies (ADA) to avalglucosidase by Week 49, we recommend that you compare PK parameter values at Day 1/2 and Week 49 in these subjects who were avalglucosidase ADA-negative on Day 1/2 and avalglucosidase ADA-positive on Week 49.

We acknowledge that you will submit the PK and ADA datasets for each clinical study in the ADaM format. We request that you also submit the PK parameter dataset to the BLA.

Question 3:
The Sponsor proposes to enrich the current analysis of effect on % predicted FVC and 6MWT at Week 97 in those patients who switch from alglucosidase alfa to avalglucosidase alfa after Week 49 with data available from an additional focused data-cut 4 months after the data-cut for the PAP. This additional data-cut would capture data for up to 8 additional patients who have reached Week 97 compared to the PAP data cut point. The Sponsor proposes to add the summary of the results, from this additional data, the supporting outputs and the analysis datasets (ADaM) for %FVC (predicted) and 6MWT in an addendum to the CSR (Module 5). Does the Agency agree with this proposal?

FDA Response to Question 3:
The proposed update may be reasonable, though datasets will need to be provided no later than a month after the initial submission so that they can be reviewed in full in a reasonable time period. Please clarify your anticipated timeline for submission of the proposed addendum.

Meeting Discussion: ***Refer to attached Sponsor's response to FDA Preliminary Comments. The Sponsor clarified that they plan to include the addendum to the clinical study report (Module 5) with the supporting outputs and analysis datasets (ADaM) for %FVC (predicted) and 6MWT with the original BLA submission. No further discussion required.***

Question 4:
Does the Agency agree with the Sponsor's submission plan to provide the Agency with data on impacted study visits and data due to the COVID-19 Pandemic?

FDA Response to Question 4:
The plan to follow FDA guidance to document the COVID19 contingency measures that were implemented for management of avalglucosidase alfa study is acceptable.

Meeting Discussion: ***No further discussion required.***

Question 5:
Does the Agency agree that the electronic Common Technical Document (eCTD) Table of Content (TOC) is acceptable for the submission?

FDA Response to Question 5:
The Agency does not agree with the format for the following modules: 1.1.2, 1.1.3, 1.1.7, and 2.3.

Regarding Modules 1.1.2, 1.1.3, and 1.1.7, please note that additional nodes should not be created beyond what is in the eCTD structure specifications. Please follow *The Comprehensive Table of Contents Headings and Hierarchy*[5] for more details regarding the eCTD structure specifications. Instead, leaf titles can be used to differentiate between documents in Module 1.1.

Regarding Module 2.3 titled "Introduction," if the introduction is meant as the Introduction to Summary, it should be marked as Module 2.2. If it is the Introduction to Module 2.3, one document can be submitted under 2.3 with the leaf title "Introduction."

Regarding Modules 2.3.S and 2.3.P, you do not reference the narratives that should be included in those sections.

For further guidance on acceptable submission format per Module, please follow *Guidance for Industry: M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use.*[6]

From a technical perspective (and not content-related), the proposed organization of the other Modules is acceptable.

In Module 5, please include all SAS programming codes used to generate the efficacy and safety results of Studies EFC14028 and ACT14132 reported in their Clinical Study Reports.

[5] https://www.fda.gov/media/76444/download

[6] https://www.fda.gov/media/71551/download

Please also refer to the additional comments.

Meeting Discussion: ***Refer to attached Sponsor's response to FDA Preliminary Comments.***

FDA recommended that additional SAS programming codes be submitted for the following output and analyses in Study EFC14028:

- ***Plot of mean over time, plot of mean change from baseline over time, and summary statistics by visit for FVC and 6MWT, including both primary analysis period and extension treatment period***
- ***Sensitivity analyses for the primary efficacy endpoint in Sections 2.5.3.1 and 2.5.3.2 of the statistical analysis plan (SAP)***
- ***Subgroup analyses in Section 2.5.4 of the SAP***
- ***Patient disposition table, baseline demographic table, and baseline disease characteristic table***

The Sponsor asked whether they can submit these additional codes within 30 days after the BLA submission and still have the BLA considered complete.

Post-meeting Comment:
The additional codes may be submitted within 30 days after the BLA submission; this will not affect the determination regarding a complete NDA submission. Please see DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION in Section 3.0 OTHER IMPORTANT INFORMATION.

Question 6:
Does the Agency agree that the BLA for avalglucosidase alfa meets the criteria for Priority Review?

FDA Response to Question 6:
This will be determined during the filing review of your application.

Meeting Discussion: ***No further discussion required.***

Question 7:
Does the Agency agree that, based upon the data shared to date, an Advisory Committee is unlikely?

FDA Response to Question 7:
The Agency will determine the need for an Advisory Committee during the review of your application.

Meeting Discussion: ***No further discussion required.***

Question 8:
Does the Agency agree with the proposed rolling submission schedule?

FDA Response to Question 8:
Your proposed plan for a rolling submission is acceptable. We remind you that a formal rolling review request is required prior to the application submission. Refer to *Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics*.[7]

Meeting Discussion: ***No further discussion required.***

Question 9:
Does the Agency agree that the proposed submission plan constitutes a complete submission under the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs ("the Program")?

FDA Response to Question 9:
The proposed submission plan appears acceptable, but whether you have provided a complete submission will be determined during the filing review. Refer to the responses to Question 3 and Question 11.

Meeting Discussion: ***No further discussion required.***

Question 10:
Does the Agency expect to request an Application Orientation Meeting with the Sponsor?

FDA Response to Question 10:
The applicant may request an application orientation meeting (AOM) with the FDA for the purposes of orienting the review team to the content and format of the application. If an AOM is requested, the FDA will make every effort to grant the applicant's request based on the availability of resources.

Meeting Discussion: ***No further discussion required.***

Question 11 (added via email dated 6/11/20):
At the Type C meeting held on 20 February 2020, a proposal for the 120 day safety update was made in section 9.1.6 QUESTION 6: Data Cut Dates on pages 41 – 42 of the briefing package submitted on 18 December 2019, Serial 0196 and was agreed to by the Division. There was no further discussion at the meeting on his question. Will this agreement for a safety update at 120 days still stand if a request for priority review is granted?

[7] https://www.fda.gov/media/86377/download

FDA Response to Question 11:
Your proposal appears reasonable provided that the results do not meaningfully change the overall risk-benefit. A 120-day safety update would still hold.

Meeting Discussion: ***No further discussion required.***

Additional Comments

CMC

1. To facilitate the Agency's review of the drug substance and drug product manufacturing processes for alglucosidase alfa you should provide the information for all attributes, parameters, or controls proposed for routine commercial manufacturing as well as those evaluated during development and validation, in the tabular format provided below. Please provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. Note, this Table does not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

Title: INSERT UNIT OPERATION

Process parameter/ operating parameter/In-process control (IPC)/In-process tests (IPT)	Proposed Range for Commercial Manufacturing[1]	Criticality classification[2]	Tested Range from process development[1]	Manufactured Range from process validation[1]	Justification of the proposed commercial acceptable range[3] (or link to eCTD)	Comment[4]

[1]As applicable

[2]For example, critical process parameter, non-critical process parameter, as described in Module 3

[3]This could be a brief verbal description of the ranges (e.g., "development range", "validation range", or "platform experience") or links to the appropriate section of the eCTD.

[4]Optional

2. To facilitate the Agency's review of the control strategy for alglucosidase alfa you should provide information for critical quality attributes and process and product-related impurities for the drug substance and drug product in the following tabular format. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. Note, this table does not replace

other parts Module 3 or impact the nature or amount of information included in those parts of Module 3.

Critical Quality Attributes (including Process and Product related impurities for DS and DP)	Impact[1]	Source[2]	Analytical method [3]	Proposed control strategy[4]	Justification of the proposed control strategy[5]	Comment[6]

[1]What is the impact of the attribute, e.g., contributes to potency, immunogenicity, safety, efficacy

[2]What is the source of the attribute or impurity, e.g., intrinsic to the molecule, fermentation, protein A column

[3]List the methods used as part of the control strategy to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.

[4]List all the ways the attribute is controlled, e.g., in-process testing, validated removal, release testing, stability testing.

[5]This could be a brief verbal description or links to the appropriate section of the eCTD.

[6]Optional

Post-meeting Comment:
The Agency confirms that the suggestion is for the avalglucosidase product and not alglucosidase alfa.

Microbiology:
The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities

should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to, the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).
- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4).
- Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*[8].

[8] https://www.fda.gov/media/76124/download

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- Identification of the manufacturing areas and type of fill line (e.g., open, RABS, isolator), including area classifications.
- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.
- Parameters for filling and capping for the vials.
- A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Isolator decontamination summary data and information, if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.
- Information and summary results from shipping validation studies.

- Validation of capping parameters, using a container closure integrity test.
- Lyophilizer sterilization validation summary data and information.

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.
- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).
- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.
- Microbiological studies in support of the post-reconstitution and/or post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended reconstitution solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-borne infections. *In lieu* of this data, the product labeling should recommend that the post-reconstitution and/or post-dilution storage period is not more than 4 hours.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

    - Additional SAS programming codes as detailed in the Meeting Discussion for Question #5 (refer to Section 2.0 DISCUSSION above).

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT – BIOMETRICS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications

submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[9] and Pregnancy and Lactation Labeling Final Rule[10] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

[9] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information

[10] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[11] and the guidance for industry, *Identification of Manufacturing Establishments in*

[11] https://www.fda.gov/media/84223/download

Applications Submitted to CBER and CDER Questions and Answers[12]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[13]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this

[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[13] https://www.fda.gov/media/85061/download

collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ATTACHMENTS AND HANDOUTS

1) Response to FDA Preliminary Comments was provided by Genzyme via email on June 28, 2020.
2) Clarification on the PK/ADA datasets was provided by Genzyme via email on July 1, 2020, after the teleconference.

28 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNY N DOAN
07/14/2020 02:32:57 PM
Signed on behalf of Dr. Soule.

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 109569
Request Receipt Date	May 19, 2020
Product	Avalglucosidase alfa (GZ402666, neoGAA) Recombinant human α-glucosidase conjugated with synthetic bis mannose-6-phosphate-Man6 glycan
Indication	Pompe disease (acid α-glucosidase deficiency).
Drug Class/Mechanism of Action	Enzyme replacement therapy (ERT)
Sponsor	Sanofi Genzyme
ODE/Division	ORPURM/DRDMG
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	July 18, 2020

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and** will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)**.** Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Long-term use as an enzyme replacement therapy (ERT) for the treatment of patients with late-onset Pompe disease (acid α-glucosidase deficiency).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

Executive Summary

This is the second request for Breakthrough Therapy Designation (BTD) submitted to IND 109569 for the use of enzyme replacement therapy avalglucosidase alfa (neoGAA) in patients with a confirmed diagnosis of Pompe disease.

Pompe disease is a rare, serious, and life-threatening disease caused by mutations in the lysosomal acid alpha glucosidase (*GAA*) gene, resulting in glycogen accumulation. Lysosomal accumulation of glycogen leads to myocyte destruction, progressive muscle weakness, and eventual respiratory failure. The spectrum of disease includes both infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD). The clinical diagnosis of IOPD requires involvement of cardiomyopathy within the first year of life. In comparison, the clinical course of LOPD is highly variable as some patients face severe early morbidity and mortality as adolescents or young adults, whereas others face a more protracted course and may live a normal lifespan albeit with significant morbidity.

First generation enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme) was approved in April 2006 for patients diagnosed with infantile onset Pompe disease (IOPD), based upon improvement in ventilator free survival compared to the well described natural history of disease. It was subsequently approved for LOPD patients (Lumizyme) in May 2010 based on improvements in lung function (FVC % predicted) and six-minute walk distance compared to placebo. Currently, alglucosidase alfa (Lumizyme; Myozyme is no longer manufactured) is the only approved therapy for Pompe disease. However, patients with LOPD have substantial unmet medical need, as lung function and walk distance may begin to decline again after the first few years of ERT, though this is highly variable.

The development program for avalglucosidase alfa, a second generation ERT, includes studies enrolling treatment naïve patients diagnosed with LOPD, in addition to studies that enroll IOPD patients who are either treatment naïve or treatment experienced with alglucosidase alfa. The Sponsor's initial request for Breakthrough Designation was withdrawn on March 4, 2019 for the same product and indication. This initial request was based upon data from a phase 1 dose ranging study with long term extension in treatment naïve patients diagnosed with late-onset Pompe disease (LOPD). The initial request was withdrawn after a telephone conference with the Sponsor on March 1, 2019, where the Division expressed concerns regarding the interpretability of the submission, as it did not contain comparison to an adequate control. On August 14, 2019, avalglucosidase alfa was granted Fast Track designation based upon the available non-clinical evidence and the data available from the phase 1 dose ranging studies.

This second BTD request was received in May 2020 and describes data from LOPD patients enrolled in Study EFC14028, a phase 3, randomized, double blind study of 100 patients with LOPD from the primary analysis period and the extension treatment period. This study enrolled treatment naïve LOPD patients and randomized (1:1) against the current standard of care as an active comparator (alglucosidase alfa) for a primary study duration of 49 weeks.

We recommend granting breakthrough designation based on the analyses from Study EFC14028 as the data show the following:

1. Improvement in FVC (%) predicted from baseline in patients treated with avalglucosidase alfa compared to those treated with active comparator during the primary analysis period [least squares (LS) mean difference of 2.43%; 95% confidence interval (CI): (-0.13,4.99); statistical non-inferiority met (p=0.007), statistical superiority testing p=0.06].

2. Improvement in 6MWD from baseline [LS mean difference of 30.01 meters; 95% CI: (1.33, 58.69)] in patients treated with avalglucosidase alfa compared to those threated with active comparator during the primary analysis period.

Initial approval of alglucosidase alfa in LOPD patients was based upon improvement in FVC % predicted (3.4%) and 6MWD (28 meters) compared to placebo. Given that patients enrolled in Study EFC 14028 were all treatment naïve, this degree of improvement compared to first generation ERT is encouraging. The natural history of disease for LOPD patients on alglucosidase alfa is for pulmonary and gross motor capacity to plateau or slowly progress over time. While the long-term impact on disease progression with use of avalglucosidase is unknown, the Division concludes that the possibility of improvement to a higher baseline than first generation ERT is clinically significant.

In summary, the Division concludes that LOPD is serious and life-threatening, that patients have significant unmet medical need, and that the preliminary clinical evidence shows that this second generation ERT, avalglucosidase alfa, may demonstrate substantial improvement over available therapy on both pulmonary function (% predicted FVC) and ambulation (6MWD) compared to the current standard of care, alglucosidase alfa, in patients diagnosed with LOPD.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Mechanism of Avalglucosidase Alfa

Avalglucosidase alfa is a second-generation ERT for Pompe disease designed to improve receptor targeting and enzyme uptake, with the aim to improve clinical efficacy compared to the currently approved first-generation ERT alglucosidase alfa (Myozyme/Lumizyme). Avalglucosidase alfa contains two terminal synthetic bis-mannos-6-phosphate-Man6 glycans (M6P) conjugated to alglucosidase alfa through an aminooxy nitrogen carbon double bond. When compared, the protein sequence is identical, but avalglucosidase alfa contains a single M6P molecule, whereas avalglucosidase alfa is engineered to contain approximately 13 to 18 M6P glycans.

The bisphosphorylated glycans have a higher affinity to the cation-independent mannose-6-phosphate receptor (CIM6Pr) than the mono-phosphorylated glycans and improve uptake and enzymatic activity to remove cellular deposits of glycogen. Nonclinical studies showed that avalglucosidase alfa was 3-7 times more potent in the reduction of tissue glycogen than alglucosidase alfa. Improved muscle function in GAAKO mice was also noted.

Relevant Regulatory History

The relevant regulatory history for IND 109569 is summarized below in **Table 1**:

Table 1: IND 109569 Relevant Regulatory History

Date	Type of Meeting	Concerns Addressed
28-Mar-2013		IND submission
26-Apr-2013		IND was considered safe to proceed
19-Nov-2013		FDA Orphan Status granted (DRU-2013-4119)
26-Mar-2014		EMA orphan designation (EU/3/14/1251)
7-Feb-2019		BTDR submitted (1st submission)
1-Mar-2019	t-con	The request was based upon a phase 1 dose ranging study with long-term extension in treatment naïve patients diagnosed with late-onset Pompe disease (LOPD), the Agency was concerned about the interpretability of the submission as it did not contain comparison to an adequate control.
4-Mar-2019	--	Withdrawal of BTDR
14-Aug-2019	--	Fast Track designation granted based upon the non-clinical evidence and available data from the Phase 1 dose ranging studies.
20-Feb-2020	Type C Face to Face	Discussion re: SAP for Study ECF14028 The Division requested a revised SAP prior to database lock.
13-Apr-2020	Communication	Review of revised SAP sent to the Sponsor
19-May-2020	--	BTDR submitted (2nd submission)
30-June-2020	t-con	Pre-BLA meeting – *currently scheduled*

Source: DARRTS IND 109569

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Forced vital capacity (FVC % predicted) and the six-minute walk test (6MWT) are acceptable endpoints to the Division as they measure clinically relevant functions (pulmonary function and ambulation). Both endpoints, the 6MWT and FVC% predicted served as co-primary endpoints used for the traditional approval of Lumizyme (alglucosidase alfa) in 2010 for use in patients with LOPD (refer to Section 9 for details).

These endpoints (FVC % predicted and 6MWT) have not been used to support accelerated approval for Pompe disease or other lysosomal storage disorders. Thus far, no biomarkers have been identified that the Division would consider likely to predict a clinical benefit for Pompe disease.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Alglucosidase alfa (Lumizyme), an enzyme replacement therapy, is the only approved therapy for Pompe disease. It was approved in 2010 based upon the demonstration of a treatment effect relative to placebo of 3.4 % (95% CI: 1.3% to-5.5%) improvement in % predicted upright FVC and a 28-meter (95% CI: -1 to 52 meters) treatment effect in 6MWD. Durability of effect was noted over 12 months.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.

Avalglucosidase Development Program

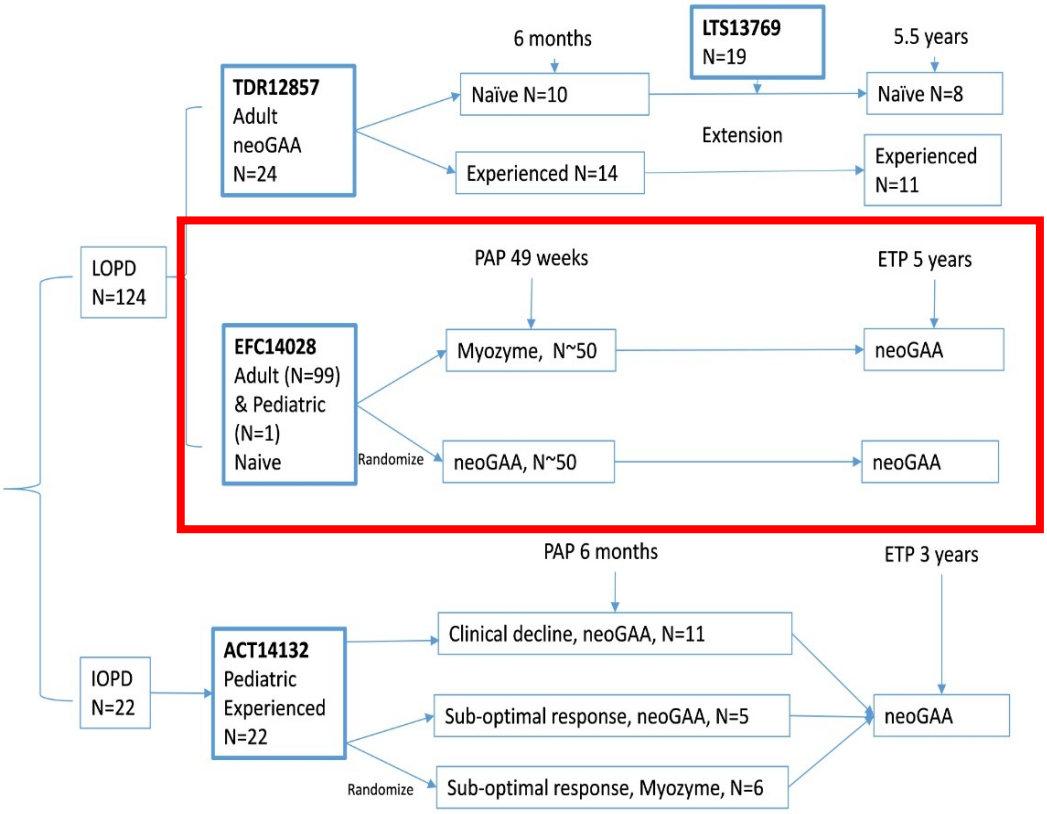
The clinical studies submitted to IND 109569 to support the development of avalglucosidase alfa in Pompe disease (b) (4) LOPD) are depicted in Table 2 and Figure 1. Sanofi intends to submit a BLA based upon these studies during the calendar year 2020.

Table 2: Description of Clinical Studies in the Avalglucosidase Development Program to be Submitted with in the BLA

Trial # /Title	Primary Objectives	Study Design	Dose	# Subjects	Completion Status
TDR12857 NEO1	PK, PD, safety Exploratory efficacy	Phase 1, OL, AD, in TN or TE adults	5,10, 20 mg/kg QOW 13 infusions	24 patients (LOPD)	Completed
LTS13769 NEO-EXT	PK, PD, safety, exploratory efficacy	OL extension TDR12857 adults	20 mg/kg QOW	19 patients (LOPD)	Ongoing
EFC14028 COMET	Efficacy, *(Primary: FVC % predicted 1st Key Secondary: 6MWD*) safety, PK, PD	Phase 3, DB with active comparator in patients ≥ 3 years to adults	20 mg/kg QOW for 12 months or more (extension)	~100 patients (LOPD)	Ongoing
ACT14132 Mini-COMET	Safety, PK, PD, Exploratory efficacy	Phase 2, OL for patients (<18 years) with clinical decline or sub-optimal response on current standard of care	20 mg/kg or 40 mg/kg QOW 24 weeks + extension	22 patients (IOPD)	Ongoing

Source: IND 109569 Pre-BLA Meeting request
OL = open label; AD = ascending dose; TN = treatment naïve; TE = treatment experienced; R = randomized;
DB = double blind; QOW = every other week; PK = pharmacokinetic; PD = pharmacodynamic

Figure 1: Schema of the Clinical Studies submitted to IND 109569



Source: IND 109569 Pre-BLA meeting request and BTDR

Data from Study EFC14028 (red rectangles) were submitted in this, the most recent request to support BTD for avalglucosidase. As noted in the Executive Summary, data were submitted from a total of 100 treatment naïve patients, randomized 1:1 with avalglucosidase alfa or alglucosidase alfa (Myozyme) for 49 weeks, with subsequent switchover to open-label avalglucosidase alfa in the extension phase. Fifty-one patients received avalglucosidase alfa and 49 patients received alglucosidase alfa during the primary analysis period. The primary endpoint of Study EFC14028 is the change in FVC % predicted in the upright position from baseline to 49 weeks, and the key secondary endpoint is the change in 6MWD over the same time period. Baseline patient demographics and characteristics were similar in both treatment arms and were generally representative of the LOPD population. A breakdown of discontinuations from Study EFC14028 is noted in Table 2. At the time of data cut off on March 19, 2020, 91 patients remain in the ETP.

Table 3: Summary of Discontinuations from Study EFC14028

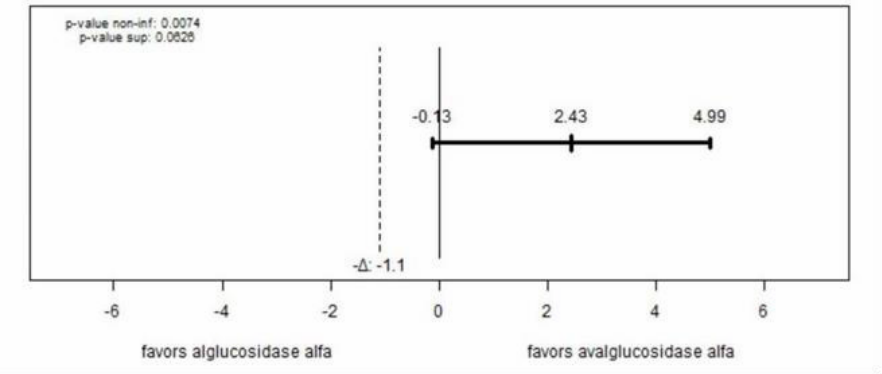
Study EFC14028	Study Arm	Reason for discontinuation
Primary analysis period (PAP) N=100	Avalglucosidase alfa: 0	--
	Alglucosidase alfa: 5	Adverse Event (4) Other (1)
Extension treatment period (ETP) -- Refers to original randomization N=95	Avalglucosidase alfa: 3	Adverse Event (2) Other (1)
	Alglucosidase alfa: 1	Adverse Event (1)

Source: IND 109569 BTDR

As previously discussed with the Agency, a mixed model for repeated measures (MMRM) was used to estimate the difference between both study arms for assessment of mean change in FVC%. The Sponsor initially evaluated non-

inferiority (NI) of avalglucosidase alfa versus alglucosidase alfa at a two-sided 5% level of significance with a pre-defined lowered level NI margin of -1.1. As this was met, the study was declared positive with at least squares (LS) mean difference of 2.43%; 95% confidence interval (CI): (-0.13,4.99); statistical non-inferiority (p=0.007). Superiority testing was performed and resulted in p=0.06 in favor of avalglucosidase alfa. Figure 2 shows the resultant analysis for NI and superiority in the primary endpoint during the PAP.

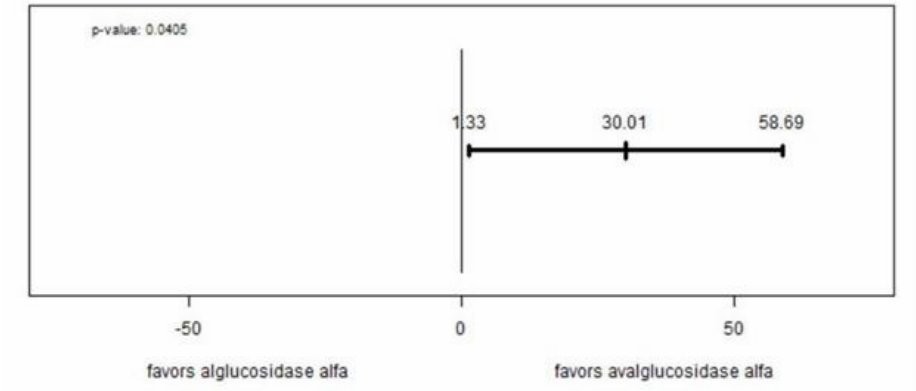
Figure 2: Forest plot for Change from baseline to Week 49 of the PAP in FVC (%) predicted



Source: IND 109569; BTDR package (Figure 3; page 16)

The first key secondary endpoint (6MWD) was also evaluated for differences between the two study arms, and the analyses suggested improved efficacy in avalglucosidase alfa over alglucosidase alfa [LS mean difference of 30.1 meters (95%CI: (1.33, 58.69)] as shown in Figure 3.

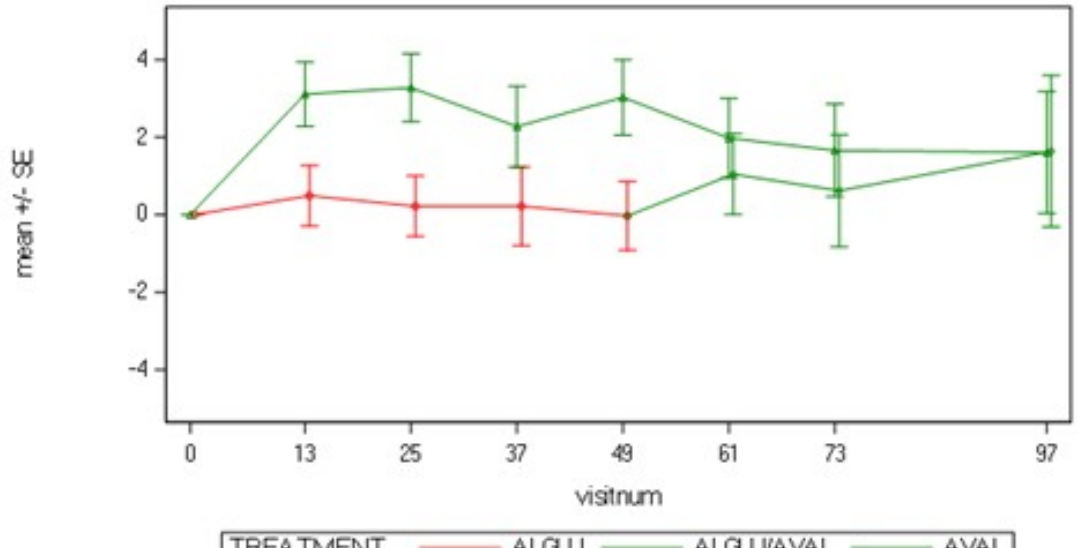
Figure 3: Forest plot for Change from baseline to Week 49 of the PAP in 6MWT (meter)



Source: IND 109569; BTDR package (Figure 6; page 18)

The Sponsor also evaluated the change from baseline of avalglucosidase alfa on pulmonary function and 6MWD over time, to include both the randomized primary analysis period (PAP) and the open-label extension trial period (ETP) in these LOPD patients. The mean change with 95% confidence intervals is noted in Figures 4 and 5 and demonstrate improvement from baseline at 49 weeks for both FVC (% predicted) and 6MWD. In addition, the patients initially randomized to alglucosidase alfa during the PAP demonstrated improvement in both endpoints upon cross-over to avalglucosidase alfa, over a similar time period.

Figure 4: Study EFC 14028 FVC (% Predicted) change from baseline over time (PAP and ETP)

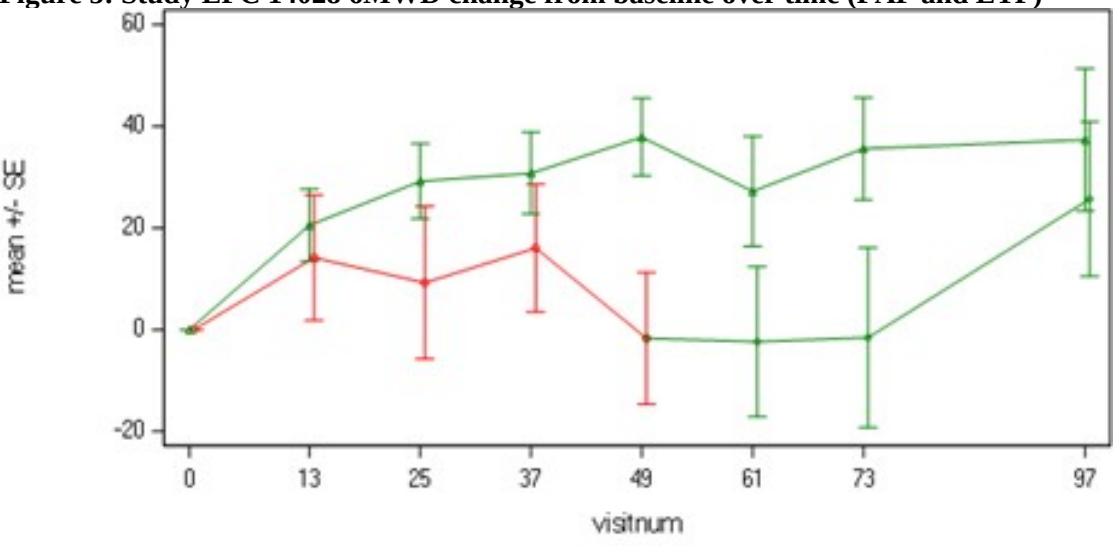


Number of Patients								
ALGLU	49	47	45	44	43			
ALGLU/AVAL					43	35	29	21
AVAL	51	51	51	51	49	41	36	24

Note: Patients in the ALGLU arm who received alglucosidase alfa in PAP were switched to avalglucosidase alfa treatment after the 49 week PAP.

Source: IND 109569; BTDR package (Figure 4; page 17)

Figure 5: Study EFC 14028 6MWD change from baseline over time (PAP and ETP)



Number of Patients								
ALGLU	49	47	45	45	43			
ALGLU/AVAL					43	36	29	22
AVAL	51	51	49	50	48	42	38	24

Note: Patients in the ALGLU arm who received alglucosidase alfa in PAP were switched to avalglucosidase alfa treatment after the 49 week PAP.

Source: IND 109569; BTDR package (Figure 7; page 19)

The safety profiles were similar in both ERT, as might be expected, though only patients receiving alglucosidase alfa reported treatment emergent adverse events (TEAEs) leading to permanent treatment discontinuation or death. In general,

fewer patients experienced severe adverse events in the avalglucosidase alfa arm (11.8%) compared with the alglucosidase alfa arm (14.3%) and 27.5% of the patients treated with avalglucosidase alfa and 32.7% of the patients treated with alglucosidase alfa experienced at least one protocol defined infusion associated reaction (IAR) in the PAP.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Overall, the data from Study EFC14028, shows improvement in FVC % predicted and 6MWD in treatment naïve LOPD patients given avalglucosidase alfa compared to alglucosidase alfa. This improvement is also seen in patients who switched over from alglucosidase alfa during the long-term extension period of the study, suggesting improvement in clinically relevant functions compared to the current standard of care (alglucosidase alfa). The preliminary analysis is supported by non-clinical evidence that demonstrated improved circulating half-life and tissue distribution (refer to Fast Track Designation). Based upon these results, DRGMG believe that avalglucosidase alfa demonstrates the potential to address an unmet medical need in patients diagnosed with Pompe disease.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

The Division recommends granting BTD to IND 109569. The Sponsor has a pre-BLA meeting with DRDMG in June 2020. As the SAP has already been reviewed, additional details for filing the BLA will be discussed then. The pediatric development program for patients diagnosed with IOPD will also be discussed in June 2020, in a separate meeting.

14. List references, if any:

- Lumizyme Label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125291lbl.pdf
- Refer to IND 109569 Fast Track Designation and the IND 127387 Breakthrough Designation requests.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?
YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

The Medical Policy and Program Review Council reviewed the breakthrough therapy designation (BTD) request for IND 109569 via email and agrees with DRDMG's recommendation to grant BTD. This concurrence was communicated to DRDMG on June 2, 2020.

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 3/18/19/M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DINA J ZAND
06/02/2020 04:23:00 PM

KATHLEEN M DONOHUE
06/03/2020 07:17:52 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109569

MEETING MINUTES

Genzyme Corporation
Attention: Jennifer Eaddy
Associate Director
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Eaddy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for neoGAA (recombinant human α-glucosidase conjugated with synthetic bis-mannose-6-phosphate-Man6 glycan).

We also refer to the meeting between representatives of your firm and the FDA on September 8, 2015. The purpose of the meeting was to discuss the overall development program for neoGAA, in (b) (4) late-onset Pompe disease (LOPD) patients in support of a future BLA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-9651.

Sincerely,

{See appended electronic signature page}

Lisa N. Pitt, PharmD, MSJ
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: September 8, 2015
Meeting Location: White Oak Building 22, Conference Room: 1419

Application Number: 109569
Product Name: neoGAA
Indication: Pompe Disease
Sponsor/Applicant Name: Genzyme

Meeting Chair: Dragos Roman
Meeting Recorder: Lisa Pitt

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products
Donna Griebel, MD, Division Director
Dragos Roman, MD, Acting Associate Division Director
Laurie Muldowney, MD, Acting Medical Team Leader
Dina Zand, MD, Medical Reviewer
David Joseph PhD, Pharmacology Team Leader
Lisa Pitt, PharmD, MSJ, Senior Regulatory Project Manager

Office of Clinical Pharmacology/Division of Pharmacology III
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader
Christine Hon, PhD, Clinical Pharmacology Reviewer

Office of Biotechnology Products
Christopher Downey, PhD, Product Quality Team Leader
Simon Williams, PhD, Product Quality Reviewer

Office of Biostatistics/Division of Biostatistics III
Min Min, Biostatistics Reviewer

SPONSOR ATTENDEES

Jennifer Eaddy, Associate Director, Regulatory Affairs
Danielle Pelletier, Associate II, Regulatory Affairs
Rumana Haque-Ahmed, Associate Vice President, Regulatory Affairs
Mike Lisjak, Director, Regulatory Affairs
Mariska Mulder, Director, Regulatory Affairs EMA
Cortney Mills, Manager, Global Regulatory CMC Biologic Products
Ged Short, Senior Medical Director, Clinical Research
Khazal Paradis, Senior Vice President, Clinical Research
Rand Sutherland, Associate Vice President, Development Innovation
Yi Xu, Director, Biostatistics and Programming
Steve Lake, Associate Vice President, Biostatistics and Programming
Kerry Culm-Merdek, Director, Clinical Pharmacology
Raheel Shafi, Director, Global Patient Safety
Patrick Finn, Associate Director, Biologics, Pharmacology & Pharmacokinetics
Lynn Davenport, Director, Preclinical Safety

1.0 BACKGROUND

Genzyme requested a Type B meeting to discuss the overall development program for neoGAA, specifically the nonclinical data package (completed, ongoing, and planned studies), the clinical data results from the Phase 1/2 clinical study, and the planned Phase 2 and Phase 3 studies in infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD) patients (b) (4)

FDA sent Preliminary Comments to Genzyme on September 4, 2015. Genzyme provided slides in advance of the meeting indicating their preference to discuss Questions 2, 3, 5, 6 and 8. Questions 1, 4, 7, 9, and 10 were not discussed; however, Genzyme has indicated agreement to conduct a fertility study and EFT rabbit study as recommended, and plan to submit a carcinogenicity position paper in advance of a BLA filing. Genzyme plans to address FDA comments in the statistical analysis plan for the Phase 3 study (see attached Sponsor presentation slides, Section 4).

2. DISCUSSION

1. Does the Agency agree that the toxicology program supports the Phase 3 clinical development program and future MAA of neoGAA administered via the IV route for the proposed Pompe disease indication in adult and pediatric populations?

   FDA Response:

   We agree that the toxicology program is adequate to support the Phase 3 development program and a BLA submission. However, we will determine whether the juvenile mouse toxicology study provides a reasonable assurance of safety for

your proposed studies in pediatric patients, based on our review and evaluation of the full report.

Additional Comments:

Your proposed timeline for conducting and submitting reproductive and developmental toxicity studies is acceptable. We strongly recommend that each of these studies be conducted using a vehicle control group and a diphenhydramine control group, because of the expected strong hypersensitivity reactions and the need for co-administration of diphenhydramine to control these reactions in nonclinical studies with ERTs.

Sponsor's (b) (4) ***fertility study in mice:***

You stated that fertility and early embryonic development was evaluated in the 9-week juvenile mouse toxicity study. However, the dosing frequency in this study was once every 2 weeks, with discontinuation of treatment prior to mating, whereas the dosing frequency in the fertility and early embryonic development studies with marketed ERT products ranged from once daily to every 3 or 4 days. Your fertility study with alglucosidase alfa in mice was conducted with a dosing frequency of every other day. It is not clear that the males and females in the juvenile mouse study with neoGAA were adequately exposed to the test-article prior to mating, throughout the mating period, and through implantation for females. Given the short plasma half-life (0.5-0.74 hr) you reported for neoGAA in CD-1 mice, the limited systemic exposure to neoGAA from biweekly dosing in the juvenile mouse study limits the fertility assessment to possible effects on the developing reproductive tract in immature mice. (b) (4) ***Given the short half-life of neoGAA, we recommend a dosing frequency of once daily or every other day in the fertility and early embryonic development study in adult mature mice.***

Sponsor's (b) (4) ***embryofetal development study in rabbits:***

(b) (4) ***an embryofetal development (EFD) study in rabbits (i.e. severe maternal toxicity and absence of embryofetal effects in the rabbit study with alglucosidase alfa)*** (b) (4) ***The rabbit EFD study with alglucosidase alfa provided information that appears in the Myozyme and Lumizyme labels, despite the incidence of maternal toxicity in some of the animals. Therefore, it is reasonable to assume that a rabbit EFD study with neoGAA can provide information to support the labeling. neoGAA is qualitatively distinct from the related drug alglucosidase alfa, therefore information from developmental studies with alglucosidase alfa (Myozyme or Lumizyme) cannot be used to assess the embryofetal effects of neoGAA. Thus, you need to conduct an EFD study of***

neoGAA in rabbits. We recommend you first conduct a dose-ranging EFD study in rabbits, and you may consider the use of an increased number of animals/group in the definitive rabbit EFD study to minimize the impact of maternal toxicity on data interpretation.

Sponsor's proposed omission of carcinogenicity studies:

Your proposal to not conduct carcinogenicity studies appears acceptable. However, an assessment of the carcinogenic potential for neoGAA should be submitted in the BLA (see ICH guidance S6(R1).

2. Does the Agency agree that the outlined development plan in LOPD (b) (4) supports a proposed indication of "long term use as an ERT for the treatment of patients with a confirmed diagnosis of Pompe disease (acid alpha-glucosidase deficiency)"? Specifically, does the Agency agree that the inclusion of pediatric patients (b) (4) Phase 3 Study EFC14028 in LOPD (covering ages of 1-18 years) would support demonstration of efficacy and safety of neoGAA in all pediatric patients with Pompe disease?

FDA Response:

We do not agree that the outlined development program will provide sufficient data to support the demonstration of efficacy and safety of neoGAA in all pediatric patients with Pompe disease (b) (4) ***LOPD). As described, the outlined development plan might support a proposed indication of "long term use as an ERT for the treatment of patients with a confirmed diagnosis of late onset Pompe disease (acid alpha-glucosidase deficiency)" if a number of issues are adequately addressed:***

- ***<u>Proposed Phase 3 LOPD Study:</u> We agree that the outlined development program might support a proposed indication of long term use as an ERT for the treatment of patients age 5 and older with LOPD; however, this will depend upon the actual age distribution of the patients enrolled in the proposed phase 3 study and your ability to establish a clinically meaningful change in %FVC. We note that you indicated that treatment-naïve patients under 18 years of age are quite rare (12 per year in the Pompe registry), but an adequate representation of pediatric LOPD patients will be needed in order to make a risk-benefit determination in this group.*** (b) (4) ***See also responses to Questions 5 and 6.***

Additional Nonclinical Comments:

Please refer to the response to Question 4, regarding the need for the juvenile mouse study to support the inclusion of pediatric patients under 6 years of age in your proposed phase 2 and phase 3 studies.

Discussion:

The Sponsor stated that the limitation in enrolling children less than 18 years of age in the phase 3 LOPD Study is based solely on the limited number of treatment naïve pediatric LOPD patients. For example, the Sponsor was able to enroll only 4 pediatric patients in the LOTS Study. The Division acknowledged the challenge of enrolling pediatric patients and stated that the labeling will ultimately reflect the populations studied. The Sponsor plans to change the lower enrollment age to 6 years based on the nonclinical preliminary comments provided (i.e., need for the juvenile mouse study to support inclusion of patients less than 6 years). The Division finds this acceptable.

3. Does the Agency agree that the outlined, completed and proposed clinical trials provide for an adequate safety database of neoGAA for a future MAA?

FDA Response:

Based on the information provided, it appears your safety database will include 144 patients and approximately 202 patient years of exposure. We estimate this

conservatively represents approximately 3% of the US Pompe population based on an estimated worldwide prevalence of 5 – 10,000. This may be an acceptable number of patients exposed to your product; however, should your product be approved, it is anticipated that patients with Pompe disease would be chronically administered your product for years, possibly for life. In order for us to be able to make an assessment of risk-benefit at the time of BLA submission, a reasonable number of patients having been exposed to neoGAA for at least 1 year will be needed, at the dosage level(s) intended for clinical use, with extension studies for longer periods of time ongoing at that time. Preferably this will include at least 1 year's data that is concurrently controlled, as this may be more informative in evaluating the incidence and severity of adverse events that could be a manifestation of the disease being studied (See also response to Question 5 for study duration recommendations regarding efficacy). In addition, it would also be important to have adequate representation across the age spectrum.

Discussion:

The Sponsor indicated that patients will continue to be followed by their randomized treatment for12 months, thus providing 12 months of controlled safety data. The Division agreed with this approach for collecting safety data. However the Sponsor could not confirm the number of patients that would have 12 months of controlled safety data at the time of filing, so the acceptability of the safety database at the time of submission will be a review issue.

4. Does the Agency agree that the clinical data from the Phase 1/2 Study TDR12857 and the available nonclinical data support the selection of a 20-mg/kg dose and a qow dose frequency for the Phase 3 Study EFC14028 in LOPD patient's naïve to treatment?

FDA Response:

We agree that the available clinical data support the selection of a 20 mg/kg dose and qow dose frequency for the proposed Phase 3 study. However, your proposed regimen of 20mg/kg qow is supported only for patients 6 years and older, based on the age of the animals used in the 26-week toxicity study in monkeys. Your ongoing juvenile mouse toxicity study is needed to support the inclusion of pediatric patients less than 6 years old in either of your proposed phase 2 or phase 3 studies. We will determine whether your juvenile mouse toxicity study provides a reasonable assurance of safety for your proposed dose of 20 mg/kg qow for pediatric patients less than 6 years in your phase 3 study, based on our review and evaluation of the full study report.

5. Does the Agency agree that the proposed study design of the Phase 3 Study EFC14028 is appropriate to support registration, in terms of:

   - study population,
   - study duration,
   - endpoints selected, their frequency and timing, and immunogenicity assessments?

FDA Response:

- ***Study population:*** ***We agree with the study population proposed for this phase 3 study, however, a sufficient representation of pediatric patients is needed in order to support the safety and efficacy of neoGAA in this pediatric age group. (Please refer to the answer for Question 2)***

- ***Study duration:*** ***While you suggest that 6 months may be sufficient to demonstrate superiority of your product compared with rhGAA, a longer duration (i.e., a minimum of 52 weeks) is needed to ensure durability of response.***

- ***Endpoints selected:*** (b) (4) ***As the endpoint based on the overall patients' mean change from their baseline %FVC to the end of visits can be easily affected by outliers and it cannot provide information for individual patients' performance, we recommend a binary endpoint that will capture individual patients' responding status. Whether we ultimately agree on a group mean change or a responder analysis, you will need to define a clinically meaningful criterion. One approach to help confirm the clinical meaningfulness of performance measures is to include a functional measure or global measure to help confirm that the changes measured are clinically meaningful. The goal of a global measure would be to capture the change in a patient's functional performance (overall ability, sense of wellbeing) since starting blinded study medication. Therefore positive results in your proposed secondary and tertiary objectives (e.g., PRO tool, FSS, SF-36, and PedsQL) may support the clinical meaningfulness of improvements in %FVC. Finally, it will be important to demonstrate that there is no worsening of 6MWT in comparison to the control arm.***

- (b) (4) ***We understand that Pompe is a rare disease, and recruiting a sufficient number of patients for a*** (b) (4) ***study with***

95%-95% rule can be challenging. Therefore you can consider lowering the percentage for the determination of the margin (e.g., 85%). (b) (4)

However, careful examination of whether the observed treatment effect (either response rate difference or mean change difference) is clinically meaningful is still necessary (b) (4)

- ***<u>Immunogenicity assessments:</u> The schedule of assessments table for this study specified that immunogenicity samples will be evaluated for anti-drug antibodies. However, samples will be tested for anti-neoGAA antibodies as well as anti-alglucosidase alfa antibodies according to the schedule of assessments for Study ACT14132 , which is similar to Study TRD12857. Clarify the reasons for a different testing strategy in this study.***

  In addition, we recommend that you add sample collection between 7-14 days after the first treatment to the immunogenicity sampling proposed in the study design. As described in the draft FDA Guidance: Assay Development for Immunogenicity Testing of Therapeutic Proteins, samples taken 7-14 days after exposure can help elucidate an early IgM predominant response.

  Further, you did not provide sufficient detail of the immunogenicity assays for FDA to conduct a review of the assays or provide additional comments for this meeting. Prior to the initiation of phase 3 trials, we recommend that you provide detailed descriptions of the antidrug antibody assays and neutralizing anti-drug antibody assays, including assay validation data for the neoGAA-specific assays and any other assays not previously submitted. If the anti-alglusosidase alfa assays are the same as those validated for the Myozyme and Lumizyme BLAs, provide cross-reference information describing which assays are used and where they are located in those filings. If assay validation is not complete when you start phase 3 clinical trials, you will need to collect and bank patient serum samples for testing with the validated assays. To assess whether neoGAA presents epitopes resulting in unique anti-drug antibodies, we also recommend that samples that test positive for anti-neoGAA antibodies be tested for cross-reactivity to alglucosidase alfa.

- ***<u>Pharmacokinetic sampling schedule:</u> We noted that compared to Study TRD12857, the pharmacokinetic (PK) sampling duration has been shortened from 48 hours to 24 hours post-infusion in the Principal Analysis Period and to 16 hours post-infusion in the Switch Period and the Long Term Follow-up Phase. In addition, the number of samples post-dose is fewer. According to the current protocol design, a 16-hour PK sampling schedule is insufficient to accurately characterize the elimination phase in some patients, as suggested by***

the concentration-time profiles depicted in Figure 13 of the Clinical Study Report of Study TDR12857. Therefore, we recommend that you extend the sampling duration up to at least 24 hours after the end of the infusion in Study EFC14028 to fully characterize the PK profile of neoGAA.

- ***<u>Coinciding PK and immunogenicity sampling in the Long Term Follow-up Phase:</u> You proposed to perform PK assessment at 6 months and yearly thereafter and assess immunogenicity monthly for the first 6 months and quarterly after the first 6 months. We recommend that you collect an immunogenicity sample coinciding with the pre-dose PK sample at the scheduled day of PK assessment to allow evaluation of immunogenicity impact on PK, if a sample for immunogenicity testing is not scheduled on the same day of PK sampling collection.***

  <u>PK assay:</u> As shown by the concentration-time profiles in Clinical Study Report of Study TER12857, the rapid decline of neoGAA concentrations appeared to slow down at 16 – 24 hours after the end of the infusion, and the concentrations stabilized at relatively low concentrations between 10 – 50 ng/mL for another 24 hours. This profile seems to suggest the detection of endogenous GAA at timepoints later than 16 – 24 hours by the neoGAA PK assay. We recommend that you provide information about your PK assay to show what moiety(ies) is/are measured and whether endogenous GAA is detectable by the PK assay.

<u>Discussion:</u>

The discussion focused on the planned duration of the proposed phase 3 study, as well as the clinical meaningfulness of the proposed primary endpoint. The Division re-emphasized that it is critically important to establish that the change in FVC they expect to observe in the clinical trial is clinically meaningful. (b) (4) ***The Division reiterated their recommendation for a longer primary analysis period (i.e. at least 12 months) in order to demonstrate durability of treatment effect and to increase the ability to show clinically meaningful changes.***

Based on the Division's recommendation to consider a non-inferiority design, the Sponsor proposed non-inferiority margins (see meeting slide presentation). The FDA requested additional information from the Sponsor regarding their power and sample size calculations. The Sponsor agreed to provide data supporting the assumed standard deviation (b) (4) ***sample size planning.***

The Sponsor clarified that the new PK sampling plan will end at 12 hours after the end of infusion. This decision was informed by the modeling and simulation

results using a $t_{1/2}$ value of 1 hour obtained from the completed study in LOPD patients.

Post-meeting comments (PK): We noted some degree of nonlinearity in the PK profiles of the 5 - 20 mg/kg neoGAA doses. The observed mean concentration at 16 hours (12 hours post-infusion) in the 20 mg/kg dose group was higher than that projected based on a $t_{1/2}$ value of 1 hour. Therefore, we are concerned about the reliability of the model predictions which you use to select the new PK sampling schedule. We recommend that you use the PK sampling schedules as currently proposed in the synopsis of the Phase 2 and Phase 3 studies in the meeting package.

Post-meeting comments (Immunogenicity):
Regarding our recommendation to evaluate anti-drug antibody (ADA) cross-reactivity, FDA wishes to clarify that we agree that cross-reactivity is expected because the neoGAA and rhGAA have the same protein sequence. Our intent was to recommend that you devise assays to characterize whether there are ADAs against neoGAA that are unique to neoGAA in addition to the expected cross-reactive to rhGAA ADAs. Assessing the extent to which neoGAA leads to formation of ADAs distinct from those formed against rhGAA may facilitate better interpretation of, for example, neoGAA PK data or efficacy data.

6. Does the Agency agree with the choice of the primary endpoint in LOPD patients of change in % predicted FVC from baseline to Month 6 (b) (4)

FDA Response:

We agree that respiratory function is important to patients with LOPD and may agree with the choice of primary endpoint of change in % predicted FVC from baseline relative to control. (b) (4) ***What change in %FVC is clinically meaningful to LOPD patients will need to be justified. While we understand the rationale for not including 6MWT as part of a co-primary endpoint, it should be included as a secondary endpoint, in order to ensure that there is no worsening of 6MWT in comparison to the control arm. See also response to Question 5.***

Discussion:

Please see Question 5 discussion.

7. Does the Agency agree with the sample size justification, the proposed method for analysis of the primary endpoint of % predicted FVC, and the interim analysis plan of the proposed Phase 3 Study EFC14028?

FDA Response:

Statistical Comments:

- ***For sample size planning, provide your justification for the assumptions, including the group mean difference, standard deviation (SD) and dropout rate with literature support. In particular, the assumed SD of 4.5 that you selected based on the Myozyme application does not seem appropriate because survival analysis was conducted in that application as the primary analysis and nowhere in the application is it stated that the SD was 4.5. Please provide a detailed explanation. In addition, we recommend that you re-estimate your sample size in the blinded setting during the interim analysis.***
- ***Any analysis of the secondary endpoints (i.e., 'Key' secondary endpoints) for which the results are intended to be described in the labeling need to be pre-specified and agreed upon with the review division. In addition, you need to propose a valid multiplicity procedure in order to control the overall type I error for the primary and key secondary endpoints. You also need to ensure that these endpoints will measure different domains of the disease manifestations and there is no redundancy.***
- ***For handling missing data, you have proposed to use MMRM based on missing at random (MAR) assumption to analyze the proposed continuous type of the primary endpoint. You need to provide sufficient evidence to justify that the MAR assumption is suitable. If the primary endpoint will be based on the responder analysis per our suggestion, we recommend that you impute the dropouts as non-responders in your primary analysis and perform several sensitivity analyses, including the imputations of dropouts as responders. To ensure that the conclusions are not dependent on a single method of handling missing data, you should also consider different types of missing data mechanisms. For example, you may consider methods that can handle data missing not at random (MNAR), such as pattern mixture models or selection models.***
- ***Since there are approximately 70 sites and 80 patients will be in the study, to ensure the blinding of the study, you should use centralized randomization.***

8. Does the Agency agree that the proposed study design (b) (4) is appropriate to support registration in terms of:

    - dosing cohorts and regimen,

- endpoints selected,
- study population, and
- study duration?

FDA Response:

We do not agree that the study, as designed, is sufficient to support registration (b) (4) ***Please refer to response from Question 2.***

<u>Dosing cohorts and regimen:</u> We cannot agree at this time. Please provide a rationale for including a higher dosing cohort (i.e., 40mg/kg qow) in the proposed IOPD study. In addition, your ongoing juvenile mouse toxicity study is needed to support the inclusion of pediatric patients less than 6 years old in either of your proposed phase 2 or phase 3 trials. We will determine whether your juvenile mouse toxicity study provides a reasonable assurance of safety for your proposed doses of 20 and 40 mg/kg qow for pediatric patients in your phase 2 study, based on our review and evaluation of the full study report.

<u>Endpoints selected:</u> Your proposed endpoints are acceptable for a dose ranging study in order to determine an appropriate dose for a controlled study, however, in order to be considered an adequate and well controlled trial you would need to pre-specify a primary efficacy endpoint. You could consider individualized endpoints, utilizing the eligibility criteria for clinical decline for each patient as their targeted endpoint.

<u>Study population:</u> Your study population may be appropriate, however, additional studies may need to be considered for the CRIM negative IOPD population, as well as treatment naïve IOPD patients, in order to label for this patient group.

<u>Study duration</u>: Appears appropriate and adequate for a dose ranging study.

<u>Immunogenicity sampling schedule:</u> For the proposed assessment of anti-neoGAA antibodies, we recommend that you add sample collection between 7-14 days after the first treatment with neoGAA to the proposed immunogenicity sampling plan. Refer to the response to Question 5 for additional comments on immunogenicity sampling and immunogenicity assays.

<u>Pharmacokinetic sampling schedule:</u> We noted that compared to Study TRD12857, the PK sampling duration has been shortened from 48 hours to 16 hours post-infusion and the number of post-dose samples is fewer (only 4 samples). A 16-hour sampling

schedule is insufficient to accurately characterize the elimination phase in some patients as discussed in our response to Question 5. In order to allow PK comparison between patients with different disease phenotypes, we recommend that you adopt the same PK sampling schedule as that in Study EFC14028 including the recommended extension of the sampling duration up to at least 24 hours after the end of the infusion.

Post-meeting comments: In response to the information provided on slide 20 of the meeting slides, the FDA understands the recruitment challenges in pediatric trials that include a control arm (i.e., approved dose of alglucosidase alfa of 20mg/kg qow). These could be mitigated by allowing a standard of care control arm in which patients may receive alternate dosing regimens of alglucosidase alfa (i.e. 20 mg/kg q week or 40 mg/kg qow).

Please see Question 5 discussion and post meeting comments on PK sampling plan and immunogenicity.

9. Does the Agency agree that the adult data from the Phase 1/2 Study TDR12857 and the nonclinical data support initiation of clinical trials in pediatric patients with IOPD and LOPD?

FDA Response:

We agree that the adult data from the phase 1/2 study supports initiation of clinical trials in pediatric patients with LOPD, as well as pediatric patients with IOPD who have demonstrated clinical decline or sub-optimal clinical response to alglucosidase alfa, as defined in the ACT14132 Protocol Synopsis in Appendix 4 of your Meeting Background Materials.

Additional Nonclinical Comments:

Please see response to Question 4.

10. Does the Agency agree that the data from the Phase 1/2 Study TDR12857 show an impact on the clinically meaningful endpoint of % predicted FVC? Can the Agency provide feedback on the applicability of this impact on the breakthrough criteria of "preliminary clinical evidence"?

FDA Response:

Based on the information provided, it appears that neoGAA exposure resulted in changes in %predicted FVC. However, you have not yet provided justification that the magnitude of change is clinically meaningful to patients in this population. For the purpose of breakthrough therapy designation, preliminary clinical evidence means evidence that is sufficient to indicate that the drug may demonstrate substantial

improvement in effectiveness or safety over available therapies. The data from Study TDR12857 is not sufficient to indicate substantial improvement over alglucosidase alfa, as the data are both uncontrolled and include a very small number of patients. Cross study comparisons are generally inadequate to indicate substantial improvement, particularly given the potential for bias with performance measures such as FVC, which require patient cooperation and motivation. In addition, it is not clear that the observed increments of improvements of % predicted FVC seen with neoGAA are clinically meaningful to patients in this population. A direct comparison of neoGAA with alglucosidase alfa showing clinically meaningful improvements in a clinical endpoint in this population would be needed to suggest that preliminary clinical evidence indicates a substantial improvement over available therapies. See also the FDA Guidance for Industry: Expedited Programs for Serious conditions – Drugs and Biologics, 2014.
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

3.0 Other Important Information

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

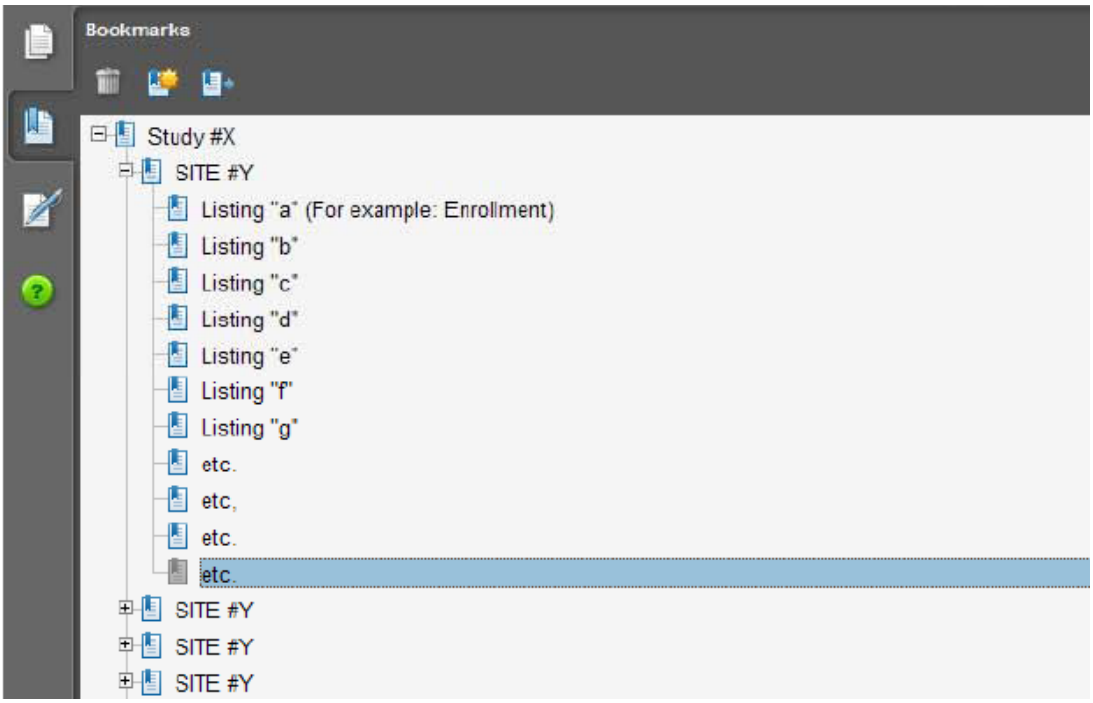
maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

4.0 ATTACHMENTS AND HANDOUTS

Sponsor meeting slides provided via email on September 8. 2015.

20 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DRAGOS G ROMAN
09/16/2015